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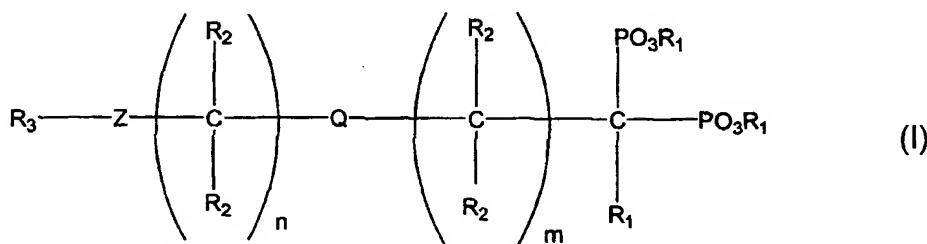
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(54) Title: **PROCESS FOR MAKING GEMINAL BISPHOSPHONATES**



(57) Abstract: The present invention relates to a novel process for making geminal bisphosphonates. The process provides for bisphosphorylation using phosphorus trihalide, phosphorous acid as a reactant/solvent, and a base as an acid acceptor/solvent. The present invention is directed to a process for making geminal bisphosphonates of the general formula (I), wherein Q is oxygen, -NR₄-, sulfur, selenium, or a single bond; m+n is an integer from 0 to about 5, Z is a ring selected from the group consisting of pyridine, pyridazine, pyrimidine, and pyrazine; R₁ is hydrogen, substituted or unsubstituted amino, amido, hydroxy, alkoxy, halogen, carboxy-
late, substituted or unsubstituted alkyl (saturated or unsaturated) having from 1 to about 6 carbon atoms, substituted or unsubstituted aryl, or substituted or unsubstituted benzyl; each R₂ is independently, hydrogen, or substituted or unsubstituted alkyl (saturated or unsaturated) having from 1 to about 4 carbon atoms; R₃ is one or more substituents selected from the group consisting of hydrogen, substituted or unsubstituted alkyl (saturated or unsaturated) having from 1 to about 6 carbon atoms, substituted and unsubstituted aryl, substituted and unsubstituted benzyl, hydroxy, halogen, carbonyl, alkoxy, nitro, amido, amino, substituted amino, carboxylate, and combinations thereof; R₄ is hydrogen, substituted alkyl (saturated or unsaturated) having from 1 to about 4 carbon atoms, or acyl.

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PROCESS FOR MAKING GEMINAL BISPHOSPHONATES

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TECHNICAL FIELD

10 The present invention relates to a novel process for making geminal bisphosphonates. The process provides for bisphosphorylation using phosphorus trihalide, molten phosphorous acid as a reactant/solvent, and a base as an acid acceptor/solvent.

CROSS REFERENCE

15 This application claims priority under Title 35, United States Code 119(e) from Provisional Application Serial No. 60/179,506, filed February 1, 2000.

BACKGROUND OF THE INVENTION

8. Polyphosphonic acids and their pharmaceutically-acceptable salts have been proposed for use in the treatment of diseases of bone and calcium metabolism. Such diseases include osteoporosis, hyperparathyroidism, hypercalcemia of malignancy, osteolytic bone metastases, myositis ossificans progressiva, calcinosis universalis, arthritis, neuritis, bursitis, tendonitis and
20 other inflammatory conditions. In particular bisphosphonates, like ethane-1-hydroxy-1,1-diphosphonic acid (EHDP), propane-3-amino-1-hydroxy-1,1-diphosphonic acid (APD), dichloromethane diphosphonic acid (Cl₂MDP), 3-amino-1-hydroxy-propylidene-diphosphonic acid. (PAMIDRONATE), 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid
25 (ALENDRONATE) and 1-hydroxy-2-(3-pyridinyl)ethylidene-1,1-bisphosphonic acid (RISEDRONATE) have been the subject of considerable research efforts in this area. Paget's disease and heterotopic ossification are currently successfully treated with EHDP. The diphosphonates tend to inhibit the resorption of bone tissue, which is beneficial to patients suffering from excessive bone loss. However, in spite of certain analogies in activity,
30 bisphosphonates do not exhibit the same degree of activity and some have serious drawbacks with respect to the degree of toxicity in animals and the tolerability or the negative side effects in humans.

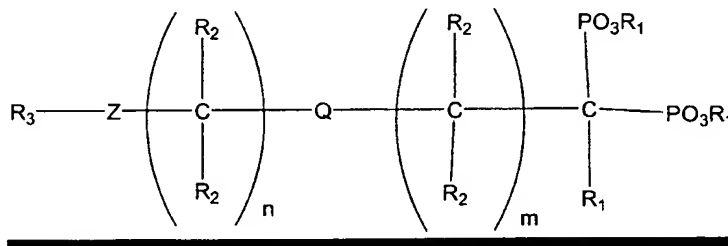
 Several methods for making bisphosphonates have been disclosed. For example, European Patent Application 0 494 644, Instituto Gentili and PCT application WO96/33199

disclose methods for making amino-bisphosphonates. However, just as there are differences in the activities of the different bisphosphonates, so too are there differences in the method of making these compounds. Depending on the reaction conditions, the viscosity of the reaction mixture and/or the formation of large amounts of elemental phosphorus by-products limit the scale on which the bisphosphorylation reaction can be readily carried out.

It is therefore desirable to use a scaleable process to produce geminal bisphosphonates that achieves high yields with little residual elemental phosphorous by-products and that can be safely practiced on the commercial scale.

SUMMARY OF THE INVENTION

The present invention is directed to a process for making geminal bisphosphonates of the general formula:



wherein Q is oxygen, -NR₄-, sulfur, selenium, or a single bond; m+n is an integer from 0 to about 5, Z is a ring selected from the group consisting of pyridine, pyridazine, pyrimidine, and pyrazine; R₁ is independently hydrogen, substituted or unsubstituted amino, amido, hydroxy, alkoxy, halogen, carboxylate, substituted or unsubstituted alkyl (saturated or unsaturated) having from 1 to about 6 carbon atoms, substituted or unsubstituted aryl, or substituted or unsubstituted benzyl; each R₂ is independently, hydrogen, or substituted or unsubstituted alkyl (saturated or unsaturated) having from 1 to about 4 carbon atoms; R₃ is one or more substituents selected from the group consisting of hydrogen, substituted or unsubstituted alkyl (saturated or unsaturated) having from 1 to about 6 carbon atoms, substituted and unsubstituted aryl, substituted and unsubstituted benzyl, hydroxy, halogen, carbonyl, alkoxy, nitro, amido, amino, substituted amino, carboxylate, and combinations thereof; R₄ is hydrogen, substituted alkyl (saturated or unsaturated) having from 1 to about 4 carbon atoms, or acyl; resulting from bisphosphorylation of an aminocarboxylic acid in the presence of phosphorus trihalide, molten phosphorous acid and base such as morpholine to form a geminal bisphosphonate.

DETAILED DESCRIPTION OF THE PRESENT INVENTION

The present invention is directed to a novel process for making geminal bisphosphonates. Said process involves the use of molten phosphorous acid, an amino carboxylic acid, phosphorous trihalide, and base in the bisphosphorylation step. The reaction is carried out at a temperature of from about 45°C to about 90°C, preferably from about 55°C to about 85°C. more preferably from about 60°C to about 75°C. The presence of an additional solvent is optional.

Particularly preferred geminal bisphosphonates made by this process are 1-hydroxy-2-(3-pyridinyl)ethylidene bisphosphonic acid, 4-amino-1-hydroxybutylidene-1,1-bisphonic acid, and 3-amino-1-hydroxypropylidene-diphosphonic acid. Most preferred is risedronate, 1-hydroxy-2-(3-pyridinyl)ethylidene-1,1-bisphosphonic acid.

10 Definitions and Usage of Terms

The following is a list of definitions for terms used herein:

As used herein, "alendronate" denotes 4-amino-1-hydroxybutylidene-1,1-bisphonic acid.

As used herein, "alkenyl" means a hydrocarbon substituent with one or more double bonds, straight or branched chain, unsubstituted or substituted.

15 As used herein, "alkoxy" means a substituent having the structure Q-O-, where Q is alkyl or alkenyl.

As used herein, "alkyl" means a saturated hydrocarbon substituent, straight or branched chain, unsubstituted or substituted.

As used herein, "alkylthio" means a substituent having the structure Q-S-, where Q is
20 alkyl or alkenyl.

As used herein, “aminocarboxylic acid” is a saturated or unsaturated substituted or unsubstituted alkyl with a carboxylic acid group attached to one end and an amine group either attached to one of the carbons of the alkyl chain or as a heteroatom in a saturated or unsaturated substituted or unsubstituted heterocyclic ring.

25 As used herein, "base" means a basic reagent which is added to a reaction mixture to facilitate bisphosphorylation. Bases include organic and inorganic bases. Preferred bases include those which have easily filterable or otherwise removable salts. Specifically, preferred bases include N,N-diisopropylethylamine, triethylamine, trimethylamine, 4-dimethylaminopyridine, pyridine, potassium carbonate, sodium carbonate, potassium bicarbonate, sodium bicarbonate and
30 morpholine. The more preferred bases are triethylamine, trimethylamine, potassium carbonate, pyridine and morpholine. The most preferred base is morpholine. The base may be added as the free base or in its salt form.

As used herein, "biohydrolyzable ester" is an ester moiety that does not interfere with the therapeutic activity of the compound, or that is readily metabolized by a human or other mammal.

As used herein, "bisphosphorylation" is the chemical reaction resulting in the production of a product containing two phosphoryl groups on the same carbon.

As used herein, "carbocyclic ring" is a saturated, unsaturated, or aromatic, hydrocarbon ring radical. Carbocyclic rings are monocyclic or are fused, bridged, or spiro polycyclic ring systems. Monocyclic rings contain from 3 to 9 atoms, preferably 4 to 7 atoms, and most preferably 5 or 6 atoms. Polycyclic rings contain from 7 to 17 atoms, preferably from 7 to 14 atoms, and most preferably 9 or 10 atoms.

As used herein, "halogen" is a chloro, bromo, fluoro, or iodo atom radical. Bromo and chloro are the most preferred halogens.

As used herein, "heterocyclic ring" is a saturated, unsaturated, or aromatic, ring radical comprised of carbon atoms and one or more heteroatoms in the ring. Heterocyclic rings are monocyclic or are fused, bridged, or spiro polycyclic ring systems. Monocyclic rings contain from 3 to 9 atoms, preferably 4 to 7 atoms, and most preferably 5 or 6 atoms. Polycyclic rings contain from 7 to 17 atoms, preferably from 7 to 14 atoms, and most preferably 9 or 10 atoms.

As used herein, "inorganic acid" is a mineral acid such as sulfuric, nitric, hydrochloric, phosphoric, and phosphorous.

As used herein, "methylene" is a $-\text{CH}_2-$ radical.

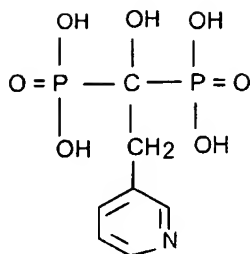
As used herein, "molten phosphorous acid" means phosphorous acid heated to from about 45°C to 95°C , preferably from about 55°C to about 85°C , more preferably from about 60°C to about 75°C .

As used herein, "organic acid" is an organic carboxylic acid, such as formic acid, acetic acid, chloroacetic acid, dichloroacetic acid, propionic acid, benzoic acid, maleic acid, fumaric acid, succinic acid, tartaric acid, and methane sulfonic acid.

As used herein, "phosphorus trihalide" is a tri-halogen substituted phosphorus. The more preferred phosphorus trihalide is phosphorus oxychloride, phosphorus oxybromide, phosphorus tribromide or phosphorus trichloride. Most preferred is phosphorus trichloride.

As used herein, "Pamidronate" denotes 3-amino-1-hydroxypropylidene-diphosphonic acid.

The term "risedronate", as used herein, denotes and 1-hydroxy-2-(3-pyridinyl)ethylidene-1,1-bisphosphonic acid and has the following structure:



The compound risedronate is further described in U.S. Patent 5,583,122, Benedict et al., assigned to the Procter & Gamble Co., issued December 10, 1996, and "An American Conference, Bisphosphonates: Current Status and future Prospects," The Royal College of Physicians, London, England, May 21-22, 1990, organized by IBC Technical Services, both references hereby are incorporated by reference.

The term "bisphosphonate active ingredient" includes the bisphosphonate free acid, bisphosphonate salts, and bisphosphonate esters, or any mixture thereof. Any pharmaceutically-acceptable, non-toxic salt or ester of bisphosphonate may be used as the risedronate active ingredient in the novel oral dosage forms of the present invention. The salts of bisphosphonate may be acid addition salts, in particular the hydrochloride, but any pharmaceutically-acceptable, non-toxic organic or inorganic acid salt may be used. In addition, salts formed with the phosphonic acid group may be used, including, but not limited to alkali metal salts (K, Na) and alkaline earth metal salts (Ca, Mg) the Ca and Na salts being preferred.

Particularly, other esters of bisphosphonate which are suitable for use as the active ingredient herein are straight chain or branched chain C₁-C₁₈ alkyl esters, including, but not limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, amyl, hexyl, heptyl, octyl, nonyl, decyl, lauryl, myristyl, cetyl, and stearyl; straight chain or branched C₂-C₁₈ alkenyl, esters, including but not limited to vinyl, alkyl, undecenyl, and linolenyl; C₃-C₈ cycloalkyl esters, including, but not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl; aryl ester, including, but not limited to phenyl, toluyl, xylyl, and naphthyl; alicyclic esters, including, but not limited to, menthyl; and arylalkyl esters, including, but not limited to benzyl, and phenethyl.

As defined above and as used herein, substituent groups may themselves be substituted. Such substitution may be with one or more substituents. Such substituents include those listed in C. Hansch and A. Leo, Substituent Constants for Correlation Analysis in Chemistry and Biology (1979), incorporated by reference herein. Preferred substituents include (for example) alkyl, alkenyl, alkoxy, hydroxy, oxo, amino, aminoalkyl (e.g. aminomethyl, etc.), cyano, halogen, alkoxy, alkoxyacyl (e.g., carboethoxy, etc.), thiol, aryl, cycloalkyl, heteroaryl, heterocycloalkyl

(e.g., piperidinyl, morpholinyl, pyrrolidinyl, etc.), imino, thioxo, hydroxyalkyl, aryloxy, arylalkyl, and combinations thereof.

As used herein, "solvent", is a substance capable of dissolving another substance to form a uniform solution. The solvent may either be polar or non-polar. Solvents for the
 5 bisphosphorylation reaction include but are not limited to inorganic acids, organic acids, and organic bases.

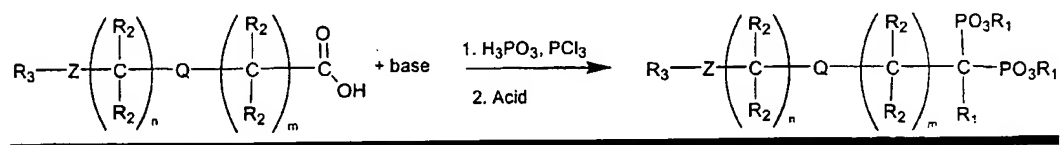
The Process

The bisphosphorylation step of the present process invention is conducted such that the corresponding aminocarboxylic acid is dissolved in molten phosphorous acid and reacted with
 10 phosphorus trihalide in the presence of a base, where the base is preferably morpholine or pyridine. The reaction is carried out in the temperature range between about 45°C to about 90°C, preferably between about 55°C to about 90°C, more preferably between about 55°C to about 85°C, and most preferably between about 60°C to about 75°C. The process described herein is readily adapted to industrial production.

Without a solvent, such as excess phosphorous acid, and a base the reaction mixture
 15 would be very viscous. The phosphorous acid and bases added in the process act as a solvent to give a uniform reaction mixture or solution. The amount of phosphorus trihalide added in relation to the aminocarboxylic acid is from about 1.7 equivalent to about 2.5 equivalents, preferably about 2 equivalents. The amount of phosphorous acid and phosphorus trihalide should
 20 be controlled to avoid the formation of pyrophoric elemental phosphorus. Phosphorus trichloride reacts with phosphorous acid under the reaction conditions consuming some of the phosphorus trichloride and liberating hydrochloric acid gas. Generally, the amount of phosphorous acid added in relation to the aminocarboxylic acid is from about 1.5 to about 6 equivalents, preferably from about 2 to about 6 equivalents, more preferably from about 2 to about 5.5 equivalents, most
 25 preferably 5 equivalents. The base is added in an amount appropriate to achieve the desired viscosity. The amount of base added in relation to the phosphorous acid is from about 0.2 to 0.8 equivalents, more preferably from about 0.4 to about 0.6 equivalents. The process described herein is readily adapted to industrial production.

This process is illustrated by the following general scheme:

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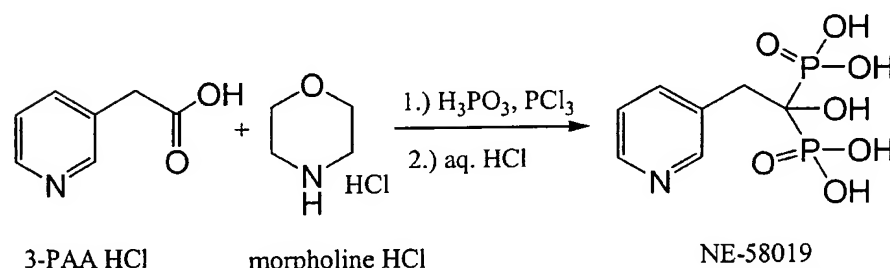


wherein Q is oxygen, -NR₄-, sulfur, selenium, or a single bond; m+n is an integer from 0 to about 5, Z is a ring selected from the group consisting of pyridine, pyridazine, pyrimidine, and pyrazine; R₁ is independently hydrogen, substituted or unsubstituted amino, amido, hydroxy, alkoxy, halogen, carboxylate, substituted or unsubstituted alkyl (saturated or unsaturated) having from 1 to about 6 carbon atoms, substituted or unsubstituted aryl, or substituted or unsubstituted benzyl; each R₂ is independently, hydrogen, or substituted or unsubstituted alkyl (saturated or unsaturated) having from 1 to about 4 carbon atoms; R₃ is one or more substituents selected from the group consisting of hydrogen, substituted or unsubstituted alkyl (saturated or unsaturated) having from 1 to about 6 carbon atoms, substituted and unsubstituted aryl, substituted and unsubstituted benzyl, hydroxy, halogen, carbonyl, alkoxy, nitro, amido, amino, substituted amino, carboxylate, and combinations thereof; R₄ is hydrogen, substituted alkyl (saturated or unsaturated) having from 1 to about 4 carbon atoms, or acyl; resulting from bisphosphorylation of an aminocarboxylic acid in the presence of phosphorus trihalide, molten phosphorous acid and base such as morpholine to form a geminal bisphosphonate.

The following non-limiting examples illustrate the processes of the present invention.

Example 1

Bisphosphorylation of 3-PAA HCl to give 1-Hydroxy-2-(3-pyridinyl)ethylidene-1,1-bisphosphonic acid



1-Hydroxy-2-(3-pyridinyl)ethylidene-1,1-bisphosphonic acid

The reaction is run on the 65 mol scale in a 30 gal reactor. The mixture of 5 eq phosphorous acid and 3-PAA·HCl, with morpholine·HCl, is melted together until complete solution is obtained at about 70-75 °C. The reaction mixture is cooled to 68 °C and 2 eq of PCl₃ is metered in over 2.5-4 hours while maintaining the temperature at 68 °C. The reaction is allowed to continue 15-30 min. after the addition is complete. Then the reaction mixture is hydrolyzed in aqueous hydrochloric

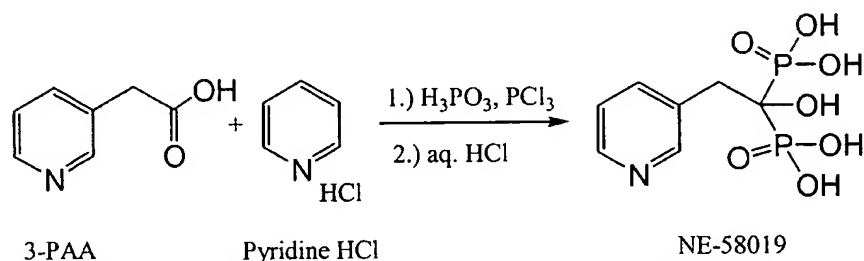
acid at 80°C for 0.5 hr to yield, after crystallization from aqueous acid/IPA, 14.2 Kg of NE-58019 in a 77.6% isolated yield.

Example 2

Bisphosphorylation of 3-PAA HCl to give 1-Hydroxy-2-(3-pyridinyl)ethylidene-1,1-

5

bisphosphonic acid

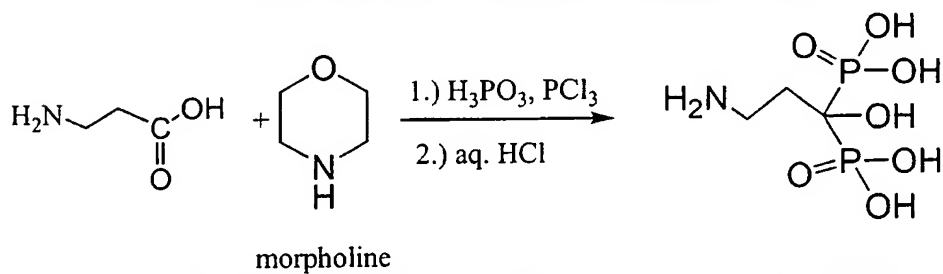


The mixture of 5 eq. phosphorous acid, 1.5 eq. pyridineHCl and 3-PAA is melted together until a uniform melt is formed (80-90°C). Then 2.1 eq. of pyridine are added. The reaction is cooled to about 70°C and 2 eq. of PCl_3 are slowly added. The mixture is heated at about 70°C for 3.5

10 hours. Water and HCl are added, the reaction hydrolyzed for about 30 to about 45 minutes at 75° C to yield risedronate after crystallization from aqueous acid/IPA.

Example 3

Bisphosphorylation of B-alanine to give pamidronate:

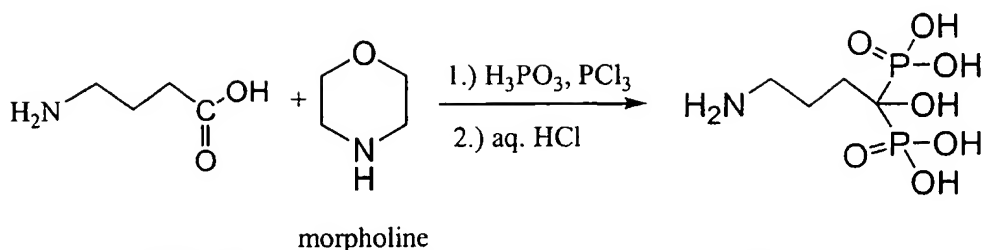


15 The mixture of 5 eq. phosphorous acid and β -alanine is heated to form a melt. Morpholine (1 eq.) is slowly added. The reaction is cooled to about 70°C and 2 eq. of PCl_3 are added. The mixture is heated for about 3.5 hours. Then the reaction is hydrolyzed in aqueous acid at about 75°C for about 0.5 hours. Crystallization from aqueous acid/IPA, affords pamidronate.

Example 4

Bisphosphorylation of 4-amino butyric acid to form 4-amino-1-hydroxybutylidene-1,1-

bisphosphonic acid



The mixture of 5 eq. phosphorous acid, 4-aminobutyric acid and morpholine • HCl is melted together until uniform solution is formed. The reaction mixture is cooled to about 70°C and 2 eq. of PCl₃ are carefully added. The mixture is heated for about 5.5 hours before the reaction mixture is hydrolyzed in aqueous acid at about 80°C. and alendronate is isolated from an ethanolic solution.

Compositions

The compounds made herein may be used in pharmaceutical compositions. The term "pharmaceutical composition" means a dosage form comprised of a safe and effective amount of an active ingredient and pharmaceutically-acceptable excipients. The pharmaceutical compositions described herein are comprised of from about, 0.1% to about 99%, preferably from about 0.5% to about 95% of an active ingredient, and from about 1% to about 99.9%, preferably from 5.00% to about 99.90% of pharmaceutically-acceptable excipients. For risedronate the composition comprises, preferably 0.25% to 40%, preferably from about 0.5% to about 30% of a risedronate active ingredient and from about 60% to about 97%, preferably from about 70% to about 99.5% of pharmaceutically-acceptable excipients.

The phrase "safe and effective amount", as used herein means an amount of a compound or composition high enough to significantly positively modify the symptoms and/or condition to be treated, but low enough to avoid serious side effects (at a reasonable benefit/risk ratio), within the scope of sound medical judgment. The safe and effective amount of active ingredient for use in the method of the invention herein will vary with the particular condition being treated, the age and physical condition of the patient being treated, the severity of the condition, the duration of the treatment, the nature of concurrent therapy, the particular active ingredient being employed, the particular pharmaceutically-acceptable excipients utilized, and like factors within the knowledge and expertise of the attending physician.

The term "pharmaceutically-acceptable excipients" as used herein includes any physiologically inert, pharmacologically inactive material known to one skilled in the art, which is compatible with the physical and chemical characteristics of the particular active ingredient selected for use. Pharmaceutically-acceptable excipients include, but are not limited to, polymers,

resins, plasticizers, fillers, lubricants, binders, disintegrants, solvents, co-solvents, buffer systems, surfactants, preservatives, sweetening agents, flavoring agents, pharmaceutical grade dyes and pigments. All or part of the pharmaceutically-acceptable excipients contained in the pharmaceutical compositions described herein is used to make the film coating which is to be
5 utilized in the novel oral dosage forms described herein.

The term "oral dosage form" as used herein means any pharmaceutical composition intended to be administered to the stomach of an individual via the mouth of said individual, and for purposes of the present invention, the preferred delivery form is in the form of a modified oval tablet (preferably film coated) containing granules or particles of active ingredient.

10 As stated hereinabove, pharmaceutically-acceptable excipients include, but are not limited to polymers, resins, plasticizers, fillers, lubricants, binders, disintegrants, solvents, co-solvents, surfactants, preservatives, sweetener agents, flavoring agents, buffer systems, pharmaceutical-grade dyes and pigments.

The preferred solvent for the pharmaceutical composition is water.

15 Flavoring agents among those useful herein include those described in *Remington's Pharmaceutical Sciences*, 18th Edition, Mack Publishing Company, 1990, pp. 1288-1300, incorporated by reference herein. Dyes, or pigments among those useful herein include those described in *Handbook of Pharmaceutical Excipients*, Second Edition pp. 126-134, 1994 by the American Pharmaceutical Association & the Pharmaceutical Press, incorporated by reference
20 herein.

Preferred co-solvents include, but are not limited to, ethanol, glycerin, propylene glycol, polyethylene glycol.

Preferred buffer systems include, but are not limited to potassium acetate, boric carbonic, phosphoric, succinic, malic, tartaric, citric, acetic, benzoic, lactic, glyceric, gluconic, glutaric and
25 glutamic. Particularly preferred are phosphoric, tartaric, citric, and potassium acetate.

Preferred surfactants include, but are not limited to, polyoxyethylene sorbitan fatty acid esters, polyoxyethylene monoalkyl ethers, sucrose monoesters and lanolin esters and ethers.

Preferred preservatives include, but are not limited to, phenol, alkyl esters of parahydroxybenzoic acid, benzoic acid and the salts thereof, boric acid and the thereof. sorbic
30 acid and the salts thereof, chlorbutanol, benzyl alcohol, thimerosal, phenylmercuric acetate and nitrate, nitromersol, benzalkonium chloride, cetylpyridinium chloride, methyl paraben, and propyl paraben. Particularly preferred are the salts of benzoic acid, cetylpyridinium chloride, methyl paraben and propyl paraben.

Preferred sweeteners include, but are not limited to, sucrose, glucose, saccharin, and aspartame. Particularly preferred are sucrose and saccharin.

Preferred binders include, but are not limited to methycellulose, sodium carboxymethylcellulose, hydroxypropylmethylcellulose, carbomer, povidone, acacia, guar gum, xanthan gum and tragacanth. Particularly preferred are methycellulose, carbomer, xanthan gum, guar gum, povidone and sodium carboxymethylcellulose.

Preferred fillers include, but are not limited to lactose, sucrose, maltodextrin, mannitol, starch, and microcrystalline cellulose.

Preferred plasticizers include, but are not limited to polyethylene glycol, propylene glycol, dibutyl phthalate, and castor oil, acetylated monoglycerides, and triacetin.

Preferred lubricants include, but are not limited to, magnesium stearate, stearic acid, and talc.

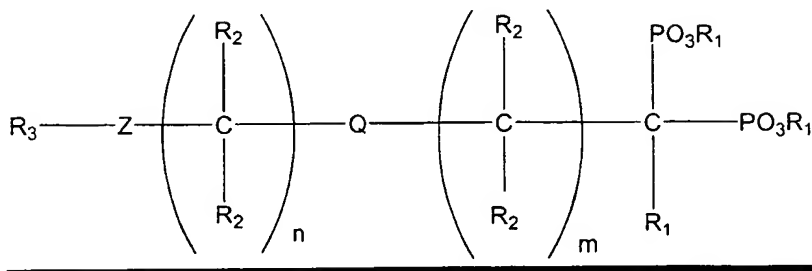
Preferred disintegrants include, but are not limited to, croscopovidone, sodium carboxymethyl starch, sodium starch glycolate, sodium carboxymethyl cellulose, alginic acid, clays, and ion exchange resins.

Preferred polymers, include but are not limited to hydroxypropylmethylcellulose (HPMC) alone and/ or in combination with hydroxypropylcellulose (HPC), carboxymethylcellulose, acrylic resins such as Eudragit® RL30D, manufactured by Rohm Pharma GmbH Weiderstadt, West Germany, methylcellulose, ethylcellulose, and polyvinylpyrrolidone or other commercially available film-coating preparations such as Dri-Klear, manufactured by Crompton & Knowles Corp., Mahwah, NJ or Opadry manufactured by Colorcon, West Point, PA.

The bisphosphonates of the present invention are generally more biologically potent in inhibiting bone resorption. Thus, the compositions of the present invention allow for greater flexibility in dosage administration and dosing intervals. For example, the compositions of the present invention, including oral compositions, may be dosed, daily, weekly, biweekly or monthly.

What is claimed is:

1. A process for making a geminal bisphosphonate of the formula:



characterized in that Q is oxygen, -NR₄-, sulfur, selenium, or a single bond; m+n is an integer from 0 to about 5, Z is a ring selected from the group consisting of pyridine, pyridazine, pyrimidine, and pyrazine; R₁ is independently hydrogen, substituted or unsubstituted amino, amido, hydroxy, alkoxy, halogen, carboxylate, substituted or unsubstituted alkyl (saturated or unsaturated) having from 1 to about 6 carbon atoms, substituted or unsubstituted aryl, or substituted or unsubstituted benzyl; each R₂ is independently, hydrogen, or substituted or unsubstituted alkyl (saturated or unsaturated) having from 1 to about 4 carbon atoms; R₃ is one or more substituents selected from the group consisting of hydrogen, substituted or unsubstituted alkyl (saturated or unsaturated) having from 1 to about 6 carbon atoms, substituted and unsubstituted aryl, substituted and unsubstituted benzyl, hydroxy, halogen, carbonyl, alkoxy, nitro, amido, amino, substituted amino, carboxylate, and combinations thereof; R₄ is hydrogen, substituted alkyl (saturated or unsaturated) having from 1 to about 4 carbon atoms, or acyl; comprising the steps of:

- a) providing an aminocarboxylic acid;
 - b) dissolving the aminocarboxylic acid in phosphorous acid; and
 - c) reacting the solution of step b) with phosphorus trihalide in the presence of a base.
2. The process of Claim 1 characterized in that the base is selected from the group consisting of N,N-diisopropylethylamine, triethylamine, trimethylamine, 4-dimethylaminopyridine, pyridine, potassium carbonate, sodium carbonate, potassium bicarbonate, sodium bicarbonate, and morpholine.
 3. The process according to any of the preceding claims characterized in that the phosphorus trihalide is selected from the group comprising phosphorus oxychloride, phosphorus oxybromide, phosphorus tribromide or phosphorus trichloride.
 4. The process according to any of the preceding claims characterized in that the phosphorous acid is heated from 45°C to 95°C until molten.

5. The process according to any of the preceding claims characterized in that the ratio of phosphorus trihalide to aminocarboxylic acid is from 1.7 to 3 equivalents.
6. The process according to any of the preceding claims characterized in that the ratio of phosphorous acid to aminocarboxylic acid is from 1.5 to 6 equivalents.
7. The process according to any of the preceding claims characterized in that the ratio of base to phosphorous acid is from 0.2 to 0.8 equivalents.
8. The process according to any of the preceding claims characterized in that the phosphorous acid is heated from 55°C to 85°C until molten.
9. The process according to any of the preceding claims characterized in that the geminal bisphosphonate is selected from the group comprising 1-hydroxy-2-(3-pyridinyl)ethylidene bisphosphonic acid, 4-amino-1-hydroxybutylidene-1,1-bisphonic acid, and (3-amino-1-hydroxy-propylidene)-diphosphonic acid.
10. The process according to any of the preceding claims characterized in that the phosphorus trihalide is phosphorus trichloride and the base is morpholine.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 01/03309

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07F9/38

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Y	DE 26 58 961 A (JOH. A. BENCKISER GMBH) 29 June 1978 (1978-06-29) example 1 ---	1-10
Y	WO 98 34940 A (APOTEX INC.) 13 August 1998 (1998-08-13) the whole document ---	1-10
Y	EP 0 350 002 A (BOEHRINGER MANNHEIM GMBH) 10 January 1990 (1990-01-10) example 1 ---	1-10
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Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- * & * document member of the same patent family

Date of the actual completion of the international search

22 June 2001

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 01/03309

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
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A	<p>KIECZYKOWSKI G. R.: "Preparation of (4-amino-1-hydroxybutylidene)bisphosphonic acid sodium salt, MK-217 (Alendronate sodium)."</p> <p>JOURNAL OF ORGANIC CHEMISTRY., vol. 60, no. 25, 1995, pages 8310-8312, XP002170341 AMERICAN CHEMICAL SOCIETY. EASTON., US ISSN: 0022-3263 the whole document</p> <p>---</p>	1-10
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